PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:
JOHN W. FREEMAN
FISH & RICHARDSON, P.C.
225 FRANKLIN STREET
BOSTON, MA 02110-2804

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing (*day/month/year*)	31 OCT 2005
Applicant's or agent's file reference 10861-034WO1	FOR FURTHER ACTION See paragraph 2 below

International application No.	International filing date (*day/month/year*)	Priority date (*day/month/year*)
PCT/US05/03104	21 January 2005 (21.01.2005)	22 January 2004 (22.01.2004)

International Patent Classification (IPC) or both national classification and IPC

IPC(7): G01N 33/00; A01K 67/00; C12N 15/00; A01N 63/00 and US Cl.: 800:3, 8, 21; 424:93.1

Applicant

THE CBR INSTITUTE FOR BIOMEDICAL RESEARCH, INC.

1. This opinion contains indications relating to the following items:

- ☒ Box No. I — Basis of the opinion
- ☐ Box No. II — Priority
- ☐ Box No. III — Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV — Lack of unity of invention
- ☒ Box No. V — Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI — Certain documents cited
- ☐ Box No. VII — Certain defects in the international application
- ☒ Box No. VIII — Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1*bis*(*b*) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA/ US	Date of completion of this opinion	Authorized officer
Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450	13 September 2005 (13.09.2005)	Joseph T. Woitach
Facsimile No. (703) 305-3230		Telephone No. (571) 272-1600

Form PCT/ISA/237 (cover sheet) (April 2005)

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US05/03104

Box No. I Basis of this opinion

1. With regard to the **language**, this opinion has been established on the basis of:

☒ the international application in the language in which it was filed

☐ a translation of the international application into _____, which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

a. type of material

☐ a sequence listing

☐ table(s) related to the sequence listing

b. format of material

☐ on paper

☐ in electronic form

c. time of filing/furnishing

☐ contained in the international application as filed.

☐ filed together with the international application in electronic form.

☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table(s) relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US05/03104

Box No. V Reasoned statement under Rule 43 *bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims 1-4, 34-36	YES
	Claims NONE	NO
Inventive step (IS)	Claims 1-4, 34-36	YES
	Claims NONE	NO
Industrial applicability (IA)	Claims 1-4, 34-36	YES
	Claims NONE	NO

2. Citations and explanations:

Claims 1-4, 34-36 lack an inventive step under PCT Article 33(3) as being obvious over Fire et al and Oberdoerffer et al. (2003).

At the time of filing the use of double stranded RNA or RNAi for affecting gene expression were well known, and used as a specific tool in research for gene discovery and establishing the function of a gene in a cell or organism (see Fire et al.). Fire et al. provide detailed guidance for making and using expression constructs for the use of RNA inhibition in characterizing a gene of interest. However, while Fire et al. teach that the system can be used in a whole organism, it does not provide the details of practicing this methodology. At the time of filing the use of transgenic animal models were known and methods of making such animals were fairly well established. At the time of filing Oberdoerffer et al. teach a Cre/Lox expression construct for the use in transgenic mice for the regulated expression of a gene of interest. The system allows for the regulated turning on or off of a gene during development, as well as for specific tissue expression (see summary in abstract and introduction). It would have been obvious to use the system detailed by Oberdoerffer et al. with the system of Fire et al. for genes that were embryonic lethal or for genes that were known to be dis-regulated in a tissue or age dependent manner, in order to establish transgenic mouse models of known diseases.

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US05/03104

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the questions whether the claims are fully supported by the description, are made:

At the time of filing methods for the generation of transgenic animals were known, however the resulting phenotype was often unpredictable. Moreover, the use of novel transgenic constructs combined with the specfic design of RNAi sequences while straightforward, would require detailed guidance depending on the particular gene of interest. The present specification sets forth an invention that is based on two elements that were not novel in the prior art, however each had their elements that required a detailed characterization for the use in specific models, including the breadth to any animal and targeting any gene.